SUMMARY MINUTES

OF THE

OPHTHALMIC DEVICES PANEL MEETING

OPEN SESSION

August 1-2, 2002

Gaithersburg Hilton
Gaithersburg, MD

OPHTHALMIC DEVICES PANEL ROSTER
AUGUST 1-2, 2002

Jayne S. Weiss, M.D.	Chair
Arthur Bradley, Ph.D.	Voting Member *
Michael R. Grimmett, M.D.	Voting Member
Alice Y. Matoba, M.D.	Voting Member
Karen Bandeen-Roche, Ph.D.	Consultant, deputized to vote
Mark A. Bullimore	Consultant, deputized to vote
Stephen A. Burns, Ph.D.	Consultant
Andrew J. Huang, M.D., M.P.H.	Consultant, deputized to vote *
Leo J. Maguire, M.D.	Consultant, deputized to vote •
William D. Mathers, M.D.	Consultant ?
Cynthia Owsley, Ph.D.	Consultant, deputized to vote
William H. Swanson, Ph.D.	Consultant, deputized to vote
Glenda V. Such, M.Ed.	Consumer Representative
Ronald E. McCarley	Industry Representative

* Primary reviewer for PMA P970043/S010
• Present on August 1, 2002 only
? Present on August 2, 2002 only

FOOD AND DRUG ADMINISTRATION (FDA) PARTICIPANTS

Everette T. Beers, Ph.D.	Chief, Diagnostic and Surgical Devices Branch
Jan C. Callaway	Team Leader
Bruce A. Drum, Ph.D.	Physicist
Malvina B. Eydelman, M.D.	Medical Officer
Donna R. Lochner	Chief, Intraocular and Corneal Implants Branch
James F. Saviola, O.D.	Chief, Vitreoretinal and Extraocular Devices Branch
Sara M. Thornton	Panel Executive Secretary
David M. Whipple	Deputy Director, Division of Ophthalmic and Ear, Nose and Throat Devices

CALL TO ORDER - AUGUST 1, 2002

Panel Chair, Jayne Weiss, M.D., called the meeting to order at 8:33 a.m.

Panel Executive Secretary Sara Thornton announced the confirmation of Dr. Jayne Weiss as Panel Chair and noted that three newly appointed voting members, Drs. Anne Coleman, Allen Ho, and Timothy McMahon, were unable to attend. Ms. Thornton then read the conflict of interest statement. Waivers had been granted to Drs. Mark Bullimore and Stephen Burns for their interests in firms that may be affected by the panel's recommendations. Dr. Burns' limited waiver allows him to participate in the panel's deliberations, but he may not vote; Dr. Bullimore may participate in the panel's deliberations and may vote. The Agency took into consideration certain matters involving Drs. Arthur Bradley, Michael Grimmett, and Jayne Weiss, who reported interests in firms at issue in matters not related to the day's agenda; the Agency has determined that they are allowed to participate fully in the panel's deliberations. Panel consultants, Drs. Karen Bandeen-Roche, Mark Bullimore, Andrew Huang, Leo Maguire, Cynthia Owsley, and William Swanson, were appointed to temporary voting status.

OPEN PUBLIC HEARING

Ronald J. Link, executive director, Surgical Eyes, Inc., noted that many patients experience complications from refractive surgery. If the panel votes to approve a premarket approval application (PMA) for the device, it should require (1) that clinical studies at multiple sites across the United States be conducted on post-refractive eyes with a minimum 1-month follow up; (2) that preexisting dry eye and large pupils be listed as a contraindication or warning in the professional and patient information booklets of any laser approved for laser in situ keratomileusis (LASIK); and (3) that postapproval studies be conducted. It is important to

identify and disclose all pre- and postoperative risk factors to both patients and doctors. In response to questions from panel members. Mr. Link said that 1-month follow up should be adequate for the studies he recommended and that the patient information booklets and the information on the FDA Web site should match.

Ms. Thornton then read a letter into the record in which the writer described the complications she experienced from refractive surgery and urged the panel to list pupil size and dry eyes as a contraindication.

David L. Shell, Arlington, VA, described the dry eyes and difficulties he has experienced since having LASIK 4 years ago. He is blind 10 percent of the time because his eyes are closed due to pain. He was not told of the high rate of dry eyes before his surgery and did not have the information before the surgery to make an informed decision. He recommended that PMA approval be conditioned on clinical studies of the incidence of LASIK-induced dry eye. In addition, the percentage of patients suffering dry eyes as a complication should be included in the patient information booklet.

OPEN COMMITTEE SESSION

David M. Whipple, deputy director, Division of Ophthalmic and Ear, Nose and Throat Devices, noted that the director of the Office of Device Evaluation, Dr. Bernard Statland, is leaving the FDA at the end of August.

James F. Saviola, O.D., chief, Vitreoretinal and Extraocular Devices Branch, presented an update on Branch activities. He noted that the Branch had recently cleared a 510(k) application for the ChromaGen Reading Aid Soft Contact Lens by Cantor & Silver Ltd. for correction of refractive ametropia or to assist people who have reading discomfort not related to

binocular vision problems or uncorrected refractive error. The clinical study did not support use of the lenses in treating dyslexia or improving reading speed and was therefore not approved for those uses. Dr. Saviola also noted that PMAs had been approved for the Paragon CRT lens for overnight orthokeratology and the Menicon Z rigid gas permeable lens for extended wear up to 30 days. Dr. Saviola summarized the devices' indications for use.

Donna Lochner, chief, Intraocular and Corneal Implants Branch, noted that the PMA for the Morcher capsular tension ring, previously reviewed at the January 2002 panel meeting, is still under review by FDA. The Agency has cleared the Ex-Press Miniature Glaucoma Implant, Models R-30 and R-50.

Everette T. Beers, Ph.D., chief, Diagnostic and Surgical Devices Branch, noted that three devices had been approved since the January 2002 panel meeting..PMA P010018s was approved on Apr;il 11, 2002, for the Refractec ViewPoint CK or conductive keratoplasty system for the temporary reduction of spherical hyperopia in patients who have 0.75 D to 3.25 D of cycloplegic spherical hyperopia. On May 17, 2002, PMA P970027/S002, Bausch & Lomb Technolas 217A excimer laser system for high myopia with astigmatism was approved. The device is indicated for the reduction or elimination of high myopia < -12 D mean refractive spherical equivalent (MRSE), where the sphere is >-7 D and < -10.99 D and the astigmatism is > 0.0D

and < -3.5 D.

In addition, a Humanitarian Device Exemption (HDE),H000002, was approved for the Custom Contoured Ablation Pattern method for the treatment of certain patients with symptomatic decentered ablations from previous laser surgery, as viewed on the Zeiss Humphrey topography unit.

PMA P970043/S010

Sponsor Presentation

Kathleen Chester, director, Regulatory Affairs, noted that the sponsor was requesting approval for the PMA for the CustomCornea™ Myopic LASIK with the LADARVision™ 4000 System device as indicated for use in Wavefront-Guided CustomCornea™ Laser In-Situ Keratomileusis (LASIK) correction for the reduction or elimination of myopia up to –7.0 D with less than –0.5 D of astigmatism at the spectacle plane in subjects who are age 21 or older.

George Pettit, M.D., Ph.D., vice president, chief scientist, Clinical Outcomes Research, defined wavefront-guided (WFG) custom ablation. The system has two components: the wavefront system and the laser. He then described wavefront sensing, which is a measurement of how the eye functions as an integrated optical system that provides a detailed refractive map within the pupil of the eye. Pettit provided technical information on how the wavefront sensor operates, using numerous slides to illustrate the differences between classical and wavefront vision testing. Calculations of wavefront are based on Zernike polynomials. Root-mean-square (RMS) wavefront error is the standard deviation of the wavefront height; if the wavefront is perfectly flat, the RMS error is zero.

Pettit then provided a detailed description of surgical wavefront measurement; he noted that the daytime pupil center is measured before dilation because the pupil center may shift with dilation. The wavefront is measured five times; the outliers are discarded, and the remaining three measurements are averaged to reach a final composite value. The wavefront and geometry information are transferred electronically to the treatment laser.

Daniel Durrie, M.D., investigator, Hunkeler Eye Clinic, Kansas City, MO, summarized the safety data. He noted that only two eyes were lost to follow up in the entire group. The safety cohort (*N* = 426 eyes) and the effectiveness subsample (*N* = 139 eyes with spherical myopia) were comparable in terms of demographics: They consisted mainly of Caucasian patients who wore soft contact lenses. The only difference between the two groups was that cylinder ranged from 0 to –0.50 in the spherical myopia cohort and ranged from 0 to –4.00 in the entire group. Durrie said that at 6-month follow up, 37 percent of the 426 eyes had gained 1 line or more in best spectacle-corrected visual acuity (BSCVA); no eyes had a BSCVA worse than 20/32. All complications were resolved, except for four eyes: One patient had epithelial ingrowth, and three experienced ghosting. All patients who had adverse events had BSCVA of 20/16 or better. No adverse events occurred in the spherical myopia group. Durrie summarized by stating that the device meets all performance limits in the guidance document and demonstrates no significant safety issues.

Omar Hakim, M.D., investigator, TLC Canada, presented effectiveness data for the 139 eyes in the study that had spherical myopia. At 1-month follow up, 97.1 percent were within 1 D of emmetropia; at 6 months, 95.7 percent of the eyes were within 1 D. Most eyes were ±1 D of emmetropia. A small amount of undercorrection occurred; more than 90 percent of eyes were within 0.5 D of the mean. The MRSE was very stable and surpassed the standards outlined in the guidance document. Visual acuity also exceeded those requirements. At 1 month, postoperative uncorrected visual acuity (UCVA was equal to or better than preoperative BSCVA) for 59 percent of the patients and at 6 months, this figure was still 52.5%.. Patients were asked to list and grade symptoms following surgery; those who noted that symptoms were worse were at –0.46 D to –0.70 D. Therefore, improvement in the rate of undercorrection may help alleviate

symptoms in future. Patient satisfaction and quality of vision both were high. Dr. Hakim summarized by saying that the device exceeds all performance limits in the guidance document and demonstrates refractive stability as defined in the guidance document.

Dr. Pettit then discussed the outcomes for the spherical myopia cohort. For almost all aberrations, the rate was statistically significantly higher postoperatively than preoperative; the finding is not surprising because LASIK tends to increase higher order aberrations. The early phase of the study had a contralateral control arm, in which patients were randomly selected to have one eye treated conventionally and one eye treated with the wavefront device. At 6 months, the conventionally treated patients had higher rates of postoperative aberrations than the wavefront group. The percentage of eyes with reduced magnitude of aberrations after surgery was greater for the wavefront group.

Stephen Brint, M.D., investigator, Brint Vision Correction Center, Metarie, LA, discussed the clinical implications of wavefront correction. He noted that higher order aberrations, particularly spherical aberration, may be substantially increased after conventional LASIK. Increased higher order aberrations after conventional LASIK have the pupil size–dependent effect of degrading retinal image quality and visual performance. Correction of higher order aberrations with an adaptive optics system improves visual acuity and contrast sensitivity. In the Custom spherical myopia cohort the percentage of eyes with a clinically significant gain in contrast sensitivity was two to threefold greater than the percentage with a clinically significant loss; with conventional treatment, no patients saw a gain and some saw a loss. For all eyes, the wavefront device showed a trend toward gain in both mesopic and photopic groups, whereas the trend with conventional treatment was toward loss. Similarly, patients treated with

the wavefront device showed a gain in low-contrast acuity: At 3 months, significantly less loss in low-contrast BSCVA occurred in the custom group than in the conventional group.

Dr. Pettit summarized by stating that the wavefront device meets all safety performance limits and exceeds all effectiveness performance limits in the FDA guidance document. Compared with conventional treatment, more eyes have a clinically significant gain than loss of contrast sensitivity, and more eyes show a gain of greater than or equal to one line of low-contrast BSCVA, rather than loss. Wavefront device–treated eyes have a statistically significantly better mean photopic contrast sensitivity, preservation of mesopic contrast sensitivity at 3 months, and statistically significantly lower loss of low-contrast BSCVA of greater than or equal to 1 line. In addition, compared with conventional treatment, WFG LASIK produces significantly fewer postoperative higher order aberrations, and significantly more wavefront-treated eyes have a reduction in higher order aberrations from the preoperative values. Dr. Pettit then provided information in response to the panel reviewers' and the FDA's questions.

Panel Questions For the Sponsor

Dr. Weiss asked whether the patients who had one type of procedure on each eye could notice a difference in vision in each eye, but Dr. Pettit said the data were not available. Panel members asked for clarification on the sample size, selection criteria, possible differences in pupil size in the two cohorts, rates of higher order aberrations and improvement in low-contrast visual acuity, implications of the higher order aberrations for later cataract surgery, and rates of patient satisfaction; sponsor representatives answered the questions to the panel's satisfaction. Dr. Pettit noted that although higher order aberrations are generally higher after LASIK surgery, with the wavefront device, they are higher by an amount than less than that with conventional surgery.

Dr. Huang observed that instead of reducing higher order aberrations, the procedure seemed to be increasing them. Dr. Durrie replied that from a clinical standpoint, the procedure is a step along the way; before, it was not possible to measure aberrations before surgery. Some surgically induced aberrations were predictable.

In response to Dr. Grimmett's comment that the patient satisfaction rate was commendable (only 9 percent were dissatisfied), Dr. Pettit said that the dissatisfied patients tended to be undercorrected. Because much hype surrounds LASIK surgery, patient expectations tend to be a bit high. Panel members concurred with Dr. Grimmett that the labeling should address patient expectations and the possibility that correction may not be 100 percent. Ronald McCarley, however, urged caution in making labeling changes designed to "placate a small segment of the population" because doing so may not affect how surgeons choose their patients. Dr. Durrie noted that the manufacturers' claims are balanced by the data. A patient who is –1.0 D has a less significant deficit than a patient who is –4.0 D; the latter are more likely to be satisfied because they start out with such a severe deficit.

Dr. Matoba commented that although the study has shown that the device is safe, it is important to compare the wavefront device against conventional treatment for patient symptoms and satisfaction. Patients' expectations will affect the level of satisfaction.

FDA PRESENTATION

Jan Callaway, FDA review team leader, provided a regulatory history of the device. The original PMA was approved in November 1998, and the sponsor is requesting approval to further expand the indication statement. In the previously approved system, the ablation pattern was based on manually entered manifest subjective refraction data for sphere and cylinder. The new

device uses information obtained from a wavefront measurement device, transferring the data via computer to the laser.

Bruce Drum, Ph.D., physicist, focused on the panel questions. He noted that the FDA has no clinical questions for the panel on the device's safety or effectiveness, but it needs the panel's input on issues specific to higher order aberration treatments, including analysis and interpretation of the results, information needed to support specific effectiveness claims, and labeling information. In addition, the FDA has questions about the differences between the wavefront-treated and the conventionally treated groups, about whether Zernicke polynomials are the most effective way to look at higher order aberrations, and about the criteria used to assess the stability of aberration corrections.

COMMITTEE DELIBERATIONS

Panel Primary Reviewers

Dr. Andrew J. Huang referred the panel to his written review. He stated that although the new surgery can treat higher order aberrations, whether the technology will work in practice is another matter altogether. Vision is a dynamic process. Using wavefront technology to correct at a given point may not be suitable for many patients, such as those who need night vision. About 90 percent of aberrations are low-order aberrations, and conventional LASIK is adequate for most patients. If we can selectively use wavefront technology for patients with higher order aberrations, the benefits can be justified. Huang said that the sponsor's study was well conducted and complimented the company on its data. He noted that the cohorts were small and asked the panel to consider whether additional safety and effectiveness data were needed before final approval. Dr. Huang pointed out that both the conventional and the WFG LASIK groups experienced an increase in higher order aberrations; the clinical significance of the difference is

unknown. About 20 percent of patients had decreased vision of greater than one line, suggesting that no additional treatment was of benefit. In addition, 10 percent of the patients said that their vision was worse than before the operation. Finally, no data in the submission discuss the long-term stability and effects of treatment.

Dr. Arthur Bradley discussed the devices' efficacy, stability, safety, aberration correction, and labeling. He noted the tendency toward undercorrection; even so, the data in the PMA exceed FDA requirements. The outcome is stable, and the device exceeds FDA's safety guidelines. WFG LASIK results in lower levels of higher order aberrations than conventional LASIK does. This improved outcome may account for the small differences seen in best corrected visual performance when compared with the conventional cohort. It is important to remember that WFG LASIK increases the level of higher order aberrations relative to preoperative levels, but less than the increase seen with conventional LASIK.

Labeling is the panel's greatest challenge. It must clearly state that that WFG LASIK does not reduce the level of higher order monochromatic aberrations relative to preoperative levels. Thus, in no way can it be thought of as a procedure to correct higher order aberrations and render supernormal vision. The sponsor can comfortably promote this process as a new LASIK procedure that is an improvement over the previous technology.

The sponsor uses the term "custom cornea," which is an appealing idea. It is now possible to sculpt the cornea to correct for inherent optical problems. Dr. Bradley challenged the sponsor to provide evidence that it had achieved this outcome. One would expect the preoperative/postoperative correlation to be zero if individual eye aberrations were perfectly corrected. We need to know the test-retest reliability to know how effective WFG LASIK is. The data leave us not knowing whether a positive correlation is due to failure to correct aberrations or

only partial correction. Dr. Bradley noted that the correlations between attempted and achieved corrections were >0.5 for third- order aberrations and were quite low for fourth-order aberrations. The evidence suggests that WFG LASIK does a better job of correcting third-order aberrations. Dr. Bradley emphasized that we do not know all of the visual ramifications of monochromatic aberrations. Vision is a polychromatic world, and it is possible that correcting aberrations might compromise vision.

In summary, the WFG LASIK system has met the efficacy, stability, and safety guidelines of the FDA. It appears to be an improvement over the already approved system

Panel Discussion of FDA Questions.

Question 1: What differences, if any, between custom and conventional outcomes are clinically and/or functionally significant? What labeling claims are supported by these differences?

Dr. Bullimore said that the sponsor has shown convincingly that the device can produce benefits. The labeling and patient information can say that the demonstrated improvements in aberrations over conventional LASIK may lead to a modest improvement in some aspects of patients' vision. Dr. Matoba noted that all the patient booklet says is that the surgery may reduce nearsightedness or eliminate the need for glasses. If that is all the sponsor wants to say, there is no need to suggest that the booklet say more. The panel agreed that it was likely that custom corneal ablation has clinical or functionally significant outcomes over conventional LASIK, but the evidence was not conclusive.

Ms. Such noted that although the wording in the patient booklet is accurate, it may lead people to conclude that the device resolves earlier problems with previous generations of LASIK. People may not understand certain phrasing, such as "refractive error." The time that is

spent going over "the eye is like a camera," is helpful, but the booklet then jumps into scientific language.

Dr. Owsley noted that no data are available on the surgery's effect on instrumental activities of daily living (IADL), such as driving. IADL problems are what patients are talking about. Dr. Grimmett said that no data support higher functional performance (IADL) or satisfaction rates in patients with customized versus conventional treatment. In addition, although data suggest that the outcome is slightly better (e.g., improved contrast sensitivity), the relation to satisfaction or IADL is unknown. There is a theoretical benefit to the performance measures.

The panel concurred that the patient brochure could say that WFG has demonstrated slightly superior optical quality (reduced monochromatic aberration) than conventional LADAR vision/LASIK and minor improvements in visual acuity and contrast sensitivity relative to conventional LADAR vision/LASIK. No data support improved functional performance.

Mr. McCarley stated that the labeling needs to make sure that it does not render obsolete all products that do not have LADAR; the comparison needs to be with conventional LADAR, not LASIK. A broad statement may not be warranted.

Mr. Whipple stated that the FDA could wordsmith the labeling statement.

Question 2: Are additional clinical data, analyses, or criteria needed to evaluate the relative effectiveness of custom and conventional treatments with regard to higher order aberrations and visual function?

Dr. Bandeen-Roche stated that there could be sources of bias with respect to the cohort, such as practice effects. Ideally, she would like to see data from randomized controlled studies.

Perhaps matched analyses could be conducted. Second, variability between sites needs to be assessed: If substantial variation exists, it means that the assessments are not valid.

The panel discussed limiting approval to treatment of people below –5.0 D, but ultimately agreed not to limit approval because it is known from prior PMAs that predictability and effectiveness fall off at higher ranges. No red flags are being raised at this point around higher ranges. In addition, the number of patients beyond –5.0 D is quite small.

Dr. Eydelman of the FDA noted that in previous approvals, the Agency has not asked sponsors to have a statistically significant number of patients in each dioptic range. Even though a small number of patients are in a high range, no safety problems have emerged. Also, this PMA represents a second generation of this device. If the panel has concerns about optical quality, they can be handled in labeling.

Several panel members noted that they would like to see the symptom and satisfaction data compared for conventionally treated patients versus wavefront-treated patients.

Question 3: What information about measurement, analysis, and correction of higher order aberrations is needed in the labeling to inform physicians and patients about safety of effectiveness of Custom Cornea treatments?

The panel agreed that the labeling should not imply that the procedure will fix everything that is wrong with a patient's vision or with current LASIK methods. The brochure should say that this kind of surgery increases aberrations postoperatively less than conventional methods. Dr. Bullimore suggested statements such as "WFG LASIK does not reduce the level of higher order aberrations of the preoperative eye" and "WFG LASIK cannot correct aberrations and provide supernormal vision." The panel members suggested that FDA staff could fine tune

the wording. The panel also thought it was important to note that the study was conducted primarily on Caucasian subjects age 65 or younger.

Question 4: What additional stability criteria are needed for higher order aberration treatments?

Dr. Bradley noted that this is a potentially important point, but the science is lagging. We know little about preoperative aberration variability, so developing criteria for postoperative aberration is difficult. Some panel members suggested that it would be reasonable to have postmarket data that tracked changes in RMS values. The panel concurred that a caveat in the data stating that no long-term data on the safety and effectiveness are available would suffice. No additional studies are required of the sponsor.

Question 5: Should stability criteria be more stringent for wavefront-based treatments than for conventional treatments?

The panel concurred that certain data tables from the sponsor's study (those that describe subjective symptoms, lines of loss, and changes in low-contrast BSCVA) should be included in the patient information booklet and that the booklet should state that vision becomes stable in the first month, not in the first weeks. If the procedure is trying to correct for small aberrations, the stability needs to be more stringent. The stability of correction for spherical myopia is the primary outcome determinant.

The panel spent additional time discussing the patient information booklet. Dr. Matoba noted that the original format of the booklet had already been improved for conventional treatment and asked whether it was fair to make the sponsor list more problems with WFG LASIK when the patient booklet for conventional LASIK will not have all that information. The

panel discussed whether the booklet for WFG should be more detailed than the booklet for conventional treatment. Dr. Eydelman noted that the booklet will have a separate section for the wavefront device. Ms. Such said that the booklet has to incorporate new knowledge and respond to consumer needs. She encouraged FDA to expand on the effects without making too much of rare instances. Mr. McCarley noted that the dry eye issue is not inherent to this application; if it is an industry issue, this PMA should not be burdened. Dr. Bullimore suggested that the panel needed to set a precedent and that perhaps the rest of industry should update its patient and physician booklets. Panel members stated that it is important to manage patient expectations and suggested that the patient information booklet should state that a certain proportion of patients will require glasses postsurgery.

OPEN PUBLIC HEARING

Mr. Link said that Surgical Eyes recommends that clinical trials be attached to this PMA. The patient labeling and patient and professional information booklets across all laser platforms need to be updated. Zernicke polynomials only extend to 6 mm pupils—large pupils are a contraindication. Information on spherical aberrations needs to be translated into patient language.

FDA COMMENTS

Mr. Whipple observed that labeling issues are challenging and that the panel has given good guidance to FDA.

SPONSOR COMMENTS

Dr. Pettit thanked the panel for its consideration.

VOTE

Ms. Thornton read the voting options to panel. The panel voted 9-0 (unanimously) that the PMA was approvable with the following conditions:

1. Issues related to clinical data
   - ?? Postoperative data should be provided to the FDA on symptoms and patient satisfaction comparing eyes treated with conventional LADARVision/LASIK compared to WFG LADARVision/LASIK treated eyes. The resulting comparison data should be included in the patient and physician labeling.
   - ?? A matched analysis of the study data comparing aberrations in conventional LADARVision/LASIK and WFG LASIK eyes
   - ?? Presentation of site to site variability in the aberration outcomes. A substantial variability would invalidate the reported confidence intervals and p values
2. The labeling in the patient and physician information booklets should include the following statements:
   - ?? WFG LASIK has demonstrated slightly superior optical quality (reduced monochromatic aberration) than conventional LADAR vision/LASIK. Minor improvements in visual acuity and contrast sensitivity relative to conventional LADAR vision/LASIK
   - ?? The accuracy of the correction for myopia is still the primary determination of uncorrected image quality and vision.

- ?? There is no data to support improved functional performance (activities of daily living such as reading, driving) or satisfaction rates in patients with WFG LASIK as compared to the conventional LADARVision/LASIK
- ?? Only a small number of eyes in the study had greater than –6.0 D refractive error (the sponsor is to provide the exact number).
- ?? Conventional LADARVision/LASIK demonstrated an increase in higher order aberrations of approximately 77 percent over preoperative levels, whereas WFG LASIK demonstrated an increase of approximately 20 percent over preoperative levels.
- ?? No retreatment data are available.
- ?? The age and race of the study population and a demographic data table
- ?? Postoperatively a patient's eyes postoperatively should achieve stable vision after one month.
- ?? The exclusion criteria in the labeling should match the exclusion criteria in the protocol

3. Tables describing the following data should be included in the patient and physician information booklets:
   - ?? Change in BSCVA
   - ?? Postoperative uncorrected visual acuity (UCVA) compared with preoperative best spectacle corrected visual acuity (BSCVA) or a statement that only 50% of patients saw well without glasses postoperatively as compared to their best preoperative spectacle correction.

- ?? The entire data table of subjective symptoms as presented in the body of the clinical study specifically including the categories of response ,i.e. significantly better, better, no change, worse, significantly worse.,

4. The patient information booklet should include the following statements:
   - ?? Preexisting dry eye condition and/or large nighttime pupils may decrease satisfaction with the LASIK procedure. Advise that patients should discuss this issue with your physician.
   - ?? The labeling should refer patients to the FDA LASIK Web site for more information.
5. The physician information booklet should include
   - ?? A table giving the Change in Low Contrast Best Spectacle Corrected Visual Acuity of the safety cohort
   - ?? List pre-existing dry eye and large nighttime pupils as a contraindication.

In explaining their votes, panel members indicated that they had reached consensus. Several panel members noted that little clinically significant difference existed between this PMA and previous submissions, and the sponsor had demonstrated safety and effectiveness of the device. Dr. Matoba noted that she hoped that the FDA would take into consideration the conditions that apply specifically to WFG LASIK so that the device is not singled out to have more stringent labeling. Ms. Such thanked the sponsor and the panel and said that the labeling changes are an improvement, not a burden. Mr. McCarley said that FDA should consider requiring all LASIK manufacturers to revise their labeling.

ADJOURNMENT

Dr. Weiss thanked the participants and adjourned the open session at 4:37 p.m.

CALL TO ORDER - August 2, 2002

Panel Chair Jayne Weiss, M.D., called the meeting to order at 8:29 a.m. E.D.T.

Panel Executive Secretary Sara Thornton announced the confirmation of the new panel chair, Dr. Jayne Weiss. Three newly appointed voting members, Drs. Anne Coleman, Allen Ho, and Timothy McMahon, were unable to attend. Ms. Thornton then read the conflict of interest statement. Panel consultants Drs. Mark Bullimore and Stephen Burns had received waivers for their interests in firms that could be affected by the panel's recommendations and could participate fully in the panel's deliberations. The Agency took into consideration certain matters concerning Drs. Arthur Bradley, Michael Grimmett, and Jayne Weiss, who reported interests in firms at issue regarding matters not related to today's agenda; they could therefore participate fully in all discussions. Ms. Thornton noted that guest speakers Drs. Henry Edelhauser, Bernard McCarey, and Liliana Werner reported interests in firms at issue.

David M. Whipple, deputy director, Division of Ophthalmic and Ear, Nose and Throat Devices, thanked the panel for its discussion on August 1, 2002, and noted that the Agency will use it in regulating the marketing and labeling of the device.

OPEN PUBLIC HEARING

John Vukich, M.D., Madison, WI, presented data comparing LASIK patients from his private practice and his investigational phakic intraocular lenses (PIOLs) patients from Staar Surgical's Implantable Contact Lens multicenter clinical trial. PIOLs offer an alternative to LASIK. With LASIK, it is not uncommon for patients to lose two lines or more of visual acuity; in his sample, not one PIOL patient lost two lines or more. PIOL may be superior to corneal ablative procedures in that patients prefer the quality of vision with PIOL. In the study, wavefront

analysis was used to assess optical quality and to compare induced aberrations; significantly more coma and spherical aberration was found in the LASIK group. Custom corneal ablation is not an option for high myopia; it removes up to 20 microns of tissue per diopter and is therefore limited to the diopter ranges that are already approved. Few options are available to patients who have high myopia or other patients for whom corneal ablation is inappropriate. A noncorneal alternative is an important step forward.

Panel members asked Dr. Vukich questions on the risks and benefits of PIOLs versus LASIK, which he answered to their satisfaction. He noted that infection is a risk; one benefit is that PIOL provides the opportunity to reverse offending treatment. In response to panel questions, Dr. Vukich stated that PIOLs should be held to the same standard as LASIK in terms of quality of vision. Small corrections can be made on the corneal level rather than going back into the eye.

OPEN COMMITTEE SESSION

General Issues Discussion

Donna Lochner, chief, Intraocular and Corneal Implants Branch, noted that the purpose of the meeting was for the panel to discuss design elements for clinical studies of phakic intraocular lenses (IOLs). The panel's recommendations will be used to further develop FDA's guidance document for phakic IOLs/ refractive implants. The panel's suggestions also will be taken into consideration by the American National Standards Institute (ANSI) and International Standards Organization (ISO) phakic IOL standards development committees.

Bernard F. McCarey, Ph.D., Emory University Eye Center, Atlanta, GA, discussed issues in clinical specular microscopy. He first described the types of equipment that are

available and the major differences between contact and noncontact microscopy. He then provided data on endothelial cell density, which diminishes over time. Cell density follows a linear regression line; at birth, a person has 3,000 to 4,000 cells per mm^2; by age 50, a person could have anywhere from 2,200 to 5,300 cells per mm^2. Surgical trauma affects cell density in the inferior, central, and superior areas; density may not return to presurgery levels. In addition, transient and chronic damage can occur from contact lens wear. Dr. McCarey described four methods of determining cell density—the comparison, frame, corner, and center methods—along with their advantages and disadvantages. Finally, he summarized issues related to the repeatability of cell density measurements. He offered suggestions for clinical trials and listed issues related to clinical site training that affect measurement of endothelial cell density.

Henry F. Edelhauser, Ph.D., Emory University Eye Center, Atlanta, GA, stated that the purpose of his presentation was to provide the panel with an understanding of the variability issues regarding specular microscopy that may bias results. He provided examples of good and poor photography to illustrate the variability in specular microscopy photography. A good image has distinct cells, enables identification of at least 150 cells, and groups cells in a uniform area. Dr. Edelhauser noted that what may be a good image for clinical purposes may not be acceptable for research. Dry eye, contact lens use, settings, keratoconus, patient compliance, age, and the training of the photographer all can affect image quality; certain conditions, such as guttata, polymegethism, injury, and low cell density (i.e., huge cells) increase the variability of images. To ensure consistency, it is best for one person to conduct the image analysis. Finally, Dr. Edelhauser summarized the consequences of under- or overcounting. Research has found that Japanese and other populations of Asian patients have higher cell density, which is an important issue for researchers. In the best of hands, the precision of cell density counts is 1.5 percent.

Sources of variability include difficulty returning to the same location, poor image quality, technician error, reader analysis, and equipment calibration. Sites should not conduct their own analysis—a central reading center should.

Panel Questions for Drs. McCarey and Edelhauser

Panel members asked many questions concerning the effects of contact lenses on endothelial cell counts and whether patients should not wear their contacts for a period before surgery. Dr. McCarey suggested that not wearing lenses for 6 months would be ideal, but the topic is complicated, given that recovery of cell density is so slow. Contact lens wearers could benefit from this surgery, so they should not be excluded; surgeons just need to be aware of the issues involving endothelial cell counts. In addition, endothelial cell density not the only indicator of corneal health. In research, however, it is best to not start with patients who have low cell counts; a normal endothelial cell population with some polymegethism is best.

Panel members also asked questions to clarify what constitutes a good image and how much variability is due to the reader versus cell density. Dr. Edelhauser said that one takes three images and uses the one that has a uniform distribution of cells across the whole screen. If all three images are good, the cell count for each image is averaged. Cell density counts are less variable when a study takes place within a single site.

Dr. McCarey suggested that for research purposes, it would be helpful to do only unilateral PIOL surgery in order to obtain information from the contralateral eye.

Liliana Werner, M.D., Ph.D., director of research, Storm Eye Institute, Charleston, SC, presented an overview of issues related to cataract formation after implantation of phakic posterior chamber IOLs. She noted that two types of fibrocellular tissue attach to the lens—A

cells and E cells—and are related to different types of opacification. She presented research findings on the evolution of IOLs, fixation and sizing, surgical implantation, the relationship between cataract and myopia, and cataractogenesis. Because anterior capsule trauma may lead to crystalline lens opacities later, it is best if the lens is not touched at all during surgery. A relation has been found between cataract and myopia; Werner presented research findings that may explain this relationship. Werner also listed several mechanisms of cataract generation after phakic posterior chamber IOL procedures, including anterior chamber reduction, increase of the aqueous flare, and peripheral or central contact with the crystalline lens. Finally, Werner presented three classification systems for cataracts and noted that ideally, any system should indicate the location of the opacity and provide an index for the degree of opacity and progression.

Panel Questions for Dr. Werner

Panel members asked questions concerning appropriate intervals for tracking cataract growth, the contribution of lens material to cataract formation, and the effects of peripheral cataracts on night vision. Dr. Werner said that the literature on all those topics is scant. Dr. Mathers asked Dr. Werner about the best method for detecting small amounts of visual impairment, and she suggested that perhaps both glare testing and contrast sensitivity should be used.

OPEN PUBLIC HEARING

No comments were made.

FDA PRESENTATION

QUESTIONS FOR THE PANEL (see attached)

QUESTION 1 Endothelial Cell Density: Dr. Michael Grimmett, Lead Responder

Dr. Grimmett noted that the literature data have limitations: They are mostly retrospective, are nonrandomized, are small, have poor follow up, and do not report endothelial analyses (i.e., coefficients of variation and hexagonality). PIOLs fall into two categories: anterior chamber and posterior chamber. The two types have implications for endothelial cell loss. Dr. Grimmett summarized the available cell loss data for different types of PIOL. Data on the relationship of cell loss to IOL type will help give guidance on clinical studies.

Dr. Grimmett presented normative endothelial cell loss data and data for cell density loss following cataract surgery and penetrating keratoplasty. He stressed that it is important to determine an acceptable cell loss rate because it relates to how big sample sizes must be.

For all phakic IOL studies, endothelial cell density measurements and morphometric analyses are mandatory; corneal pachymetry is suggested. Three years is probably a sufficient study duration for posterior chamber phakic IOLs. Dr. Grimmett said that he favors 4-year studies for higher risk factors, such as angle-supported IOLs, thicker anterior chamber IOLs, shallower anterior chamber depth, and chronic anterior chamber inflammation.

Finally, Dr. Grimmett recommended minimum endothelial cell density entry requirements, derived from calculating backward from the average cell density at age of death (based on actuarial data). He noted that if 1,500 cells/mm^2 is the desired cell density at age of death, a 2.0 percent rate of annual loss is unacceptable. A loss rate of 0.9 percent provides a better result. It is impossible to precisely determine minimum entry requirements without knowing the exact rate of endothelial cell loss per year for various types of phakic IOLs.

Panel Discussion of Question 1

Panel members asked Dr. Grimmett's opinion on using a central reading center for determining cell density; he replied that if a sponsor can validate precision and validity and show that it produces results equivalent to a reading center, use of a center should not be required.

Dr. Huang suggested that Dr Grimmett's endpoint was a bit strict because surgery takes place 5 or 10 years before death; Dr. Grimmett replied that he started with that endpoint, but the spreadsheet would not work. He used the most conservative approach.

Concerning unilateral surgery, Dr. Grimmett felt that enrolling in a 3-year study and having to wait for surgery on the other eye is an unreasonable burden to investigational patients. Historical data can provide control benchmarks, and considering his recommendations for the endothelial study design, fellow eye (non-operated) data are not critical. Other panel members concurred.

QUESTION 2 Evaluation of the Natural Lens for Cataractogenesis

Dr. William Mathers, Lead Responder

Response to Question 2, Part A: Dr. Mathers stated that all PIOLs need to be evaluated for changes in the lens. Even designs that would not touch the lens could be a problem. Any perturbation is of interest. All cataract processes need to be assessed; we have to look not just at the lens but at the source of the problem, as in anterior chamber inflammation. Flare needs to be measured as well.

*Response to Question 2, Part B: The clinical significance of a l*ens opacity is subjective, and there is not good data available correlating opacities and vision changes. Central

opacification of the anterior subcapsular area will not show up in standard visual acuity testing in a dim room. Glare testing is the most relevant approach. We need to have careful measurements of patients as they enter a study and a standardized method of evaluating glare. High glare settings should be used. Two or more lines of loss are a sufficient threshold. All lens changes should be reported. As lenses are made that do not touch the central crystalline lens, they may touch the periphery of the crystalline lens, with cells migrating posteriorally. Inflammation that occurs with the anterior chamber lens may affect the development of nuclear sclerotic opacities and needs to be monitored.

Response to Question 2, Part C: No standard quantitative measures for lens changes—meaning the visualization of the changes under the anterior capsule—exist. The examination is light dependent. High-resolution color photography is the best way to follow changes over time. A scale has been developed (the LOCS system), but it can be modified. Dr. Mathers recommended the use of digital photography.

*Response to Question 2, Part D: Evaluation of l*ens changes is less objective than the endothelial cell study, for example. One study noted some change in light transmittance that was not necessarily based on cataract. Given that phakic IOLs will be implanted for a long time period and given the possibility of chronic, subclinical inflammation; at least 3 years of follow up would be necessary, and monitoring should perhaps continue beyond that point.

Panel Discussion of Question 2.

Dr. Weiss asked Dr. Mathers what he would call a clinically significant cataract. He responded that it would involve the loss of a number of lines of acuity, with much dependent on the measurement conditions. Standard measures of vision are not adequate to pick up the changes.

At least two lines of loss by glare testing, or the loss of one line without glare testing may be an appropriate cutoff. Contrast sensitivity testing should also be considered.

Dr. Bradley commented that in glare testing, the pupil constricts so if the cataract is central, it fills a larger portion of the pupil and retinal image, increasing the visual effect. A peripheral cataract covers a small proportion of the pupil. Therefore, the glare test may not measure the true impact of a peripheral cataract. Addition of cycloplegia to the glare test may be necessary to address this, perhaps in a subset of patients.

QUESTION 3. Contrast Sensitivity Substudy: Dr. Mark Bullimore, Lead Responder

Response to Question 3, Parts A and B: It is reasonable to set the clinically significant decrease in contrast sensitivity at 0.3 log units. He felt implied that 0.3 log units was parallel to two lines acuity loss which represents adverse events or other unsatisfactory outcome. He felt the loss should be at 2 or more spatial frequencies. Dr. Bullimore said that the grading approach carries the opportunity for bias. Saying the drop should be at two or more spatial frequencies is reasonable. Letter charts should remain an option for sponsors.

Panel Discussion of Question 3, Parts A and B

The panel spent considerable time discussing issues related to measuring changes in visual acuity and whether to use grading or letter charts. Panel members noted that without knowing how much change would cause a problem in functional performance, the question of the significance of a 0.3 log unit loss is difficult to answer.

Dr. Bradley noted that just because a product is new, it does not mean that contrast sensitivity has to be measured. He supported use of contrast sensitivity or contrast acuity to document whether any corneal problems or lens opacities have degraded optical quality.

Dr. Owsley said that she knows of no convincing evidence showing that letter tests are worse than grading tests in detecting visual deficits. Many researchers who use letter tests are interested in obtaining information about the entire shape of the function. Spatial frequency testing is done in a variety of circumstances—before and after surgery, and so forth. Sound arguments exist for doing all spatial frequencies, but what information is it really providing that letter testing would not provide?

Dr. Swanson noted that Dr. Bullimore's point is an important consideration for sample size. Letter testing requires a smaller number of trials. A multichoice forced choice (i.e., letter testing) is a better option than a two-choice forced choice (i.e., grating). Letter acuity is more suitable for gathering useful data in short time period.

Panel members concurred that letter charts are more appropriate for this testing.

Dr. Bullimore stated that it would be useful if the guidance would allow other tests to be considered. Several panel members noted the dearth of evidence demonstrating that measuring spatial frequencies would matter for the devices. Other panel members said that it was important to measure the whole function. Dr. Whipple noted that a guidance document always carries options for using other tests.

Response to Question 3, Part C: The panel concurred with Dr. Bullimore that if a patient cannot read or see the highest contrast, it would have to be scored as 0, not as missing data. If a person cannot see, it does not constitute missing data. The panel also concurred that tests of contrast sensitivity should have the best test–retest reliability possible and should be brief.

PANEL DISCUSSION ON REMAINING ISSUES

Panel members discussed the appropriate duration for studies before they are presented to the panel; they were unanimous that 3 years was appropriate. Dr. Bandeen-Roche noted that at least one, possibly two, endothelial cell density evaluations should be scheduled between years 2 and 3. The panel concurred and noted that ongoing follow up for another 2 years would be appropriate.

The panel also discussed whether studies should use patients or eyes as the independent entity. For LASIK studies, each eye has been the independent entity, so 150 patients could represent 300 datapoints. Dr. Bandeen-Roche noted that statistics could be used to account for the fact that two eyes do not count the same as two people.

Dr. Weiss said that for IOLs, the first eye only was used in the primary analyses; LASIK is an exception. Ms. Lochner noted that a correlation factor between both eyes of a patient was not addressed in the guidance; all calculations are based on the idea that one patient (first eye) equals one entity. If FDA allowed one eye to equal one entity, it would need to know how correlated eyes are for outcomes.

The panel discussed issues related to sample size and loss of endothelial cell density and concurred that 300 subjects was appropriate. Dr. Bradley noted that presenters had stated that a single eye would have to have a 9 percent loss in cell density in order for researchers to be able to confirm that a change had occurred. Dr. Grimmett noted that with a cell loss of 1.9 percent per year, he would be worried that patients would develop corneal edema and suggested that the studies should be able to detect cell loss rates of 1.5 percent or lower.

Dr. Bandeen-Roche noted that a sample of 300 and a 95 percent upper confidence bound would permit a 1 percent adverse event rate, which does not meet the 0 .001 standard proposed in the guidance. Instead, a sample of 3,000 would be required. She said that the issue supports the importance of collecting postmarket data and asked, "Can the panel live with 5 percent of studies claiming an adverse event rate of 0.001 or less when it is actually higher?"

The panel discussed whether patients with low myopia should be entered into trials and concurred that it would be appropriate for IDEs to focus on higher myopes first, then lower.

ADJOURNMENT

Dr. Weiss thanked the panel members and FDA staff and adjourned the panel meeting at 2:00 p.m.